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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/660,131	09/11/2003	David H. Munn	M0351-287806	6907

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/660,131	MUNN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-48* is/are pending in the application.

4a) Of the above claim(s) *9,11,12,15 and 21-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-8,10,13,14,16-20,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/04,9/04,6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendments filed 11 September 2003 and 13 June 2006 have been entered in full. Claim 2 was cancelled. New claims 47 and 48 were added.

Applicant's election with traverse of Group III (claims 1-8, 10, 13, 14 and 16-20, drawn to a method of administering an antibody to CCR6 to a subject, wherein the site of APC recruitment comprises a tumor and/or tumor draining lymph node) in the reply filed on 13 June 2006 is acknowledged. The traversal is on the ground(s) that searching each of the Groups and species would not prove unduly burdensome.

Applicant's arguments have been fully considered but are not found persuasive. The instant Groups recite unrelated methods (administering various products to diverse patient populations, *in vitro* screening) and different products. The inventions are distinct and have acquired a separate status in the art because of their different class, search and/or recognized divergent subject matter. Each Group would require various literature searches and there is no reason to believe that the searches would be co-extensive. The requirement is still deemed proper and is therefore made FINAL. Claims 9, 11, 12, 15, 21-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 13 June 2006.

Claims 1, 3-8, 10, 13, 14, 16-20, 47 and 48 are under examination.

Information Disclosure Statement

The information disclosure statement(s)(IDS) filed 19 February 2004, 02 September 2004 and 13 June 2006 were received and comply with the provisions of 37 CFR §§1.97 and 1.98. They have been placed in the application file and the information referred to therein has been considered as to the merits. However, since the International Search Report cited therein is not a true publication, it is not fully in compliance with 37 CFR 1.97. The report will be considered but will not be printed on the face of the patent issuing from this application.

Sequence Rules

The specification is not in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations. When the description of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier (SEQ ID NO:), in the text and claims of the patent application. 37 CFR 1.821(a) presents a definition for nucleotide and/or amino acid sequences. This definition sets forth limits in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Please see MPEP section 2422.01.

The specification refers to a sequence (page 44, line 10) but does not identify the sequence by its sequence identifier. Sequences appearing in drawings should be referenced in the corresponding Brief Description thereof. See 37 C.F.R. §1.58(a) and §1.83. Appropriate correction is required.

Applicant must submit a response to this Office Action and compliance with the sequence rules within the statutory period set for response to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-8, 10, 13, 14, 16-20, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification teaches that once established, human tumors are not rejected by the immune system, a state of functional tolerance occurs, which eventually proves fatal to the host. The specification describes methods of reducing immune tolerance in a subject by reducing the recruitment of tolerance inducing antigen-presenting cells (page 1). The specification states that it would be desirable to prevent tolerogenic antigen presenting cells (APC) from inducing tolerance where such

tolerance is not therapeutically beneficial, as for example, at the site of a tumor or a tumor draining lymph node. It would be desirable to prevent the migration of tolerogenic APC to sites such as tumors, where they are detrimental, while still allowing migration of non-tolerogenic APC to those sites (page 2, line 28-page 3, line 2). The specification teaches that tolerance inducing APC express elevated levels of idoleamine 2,3-dioxygenase (IDO) (page 8, lines 27-30). The specification teaches that tolerance-inducing cells may express a variety of proteins on their surface including chemokine receptor CCR6. MIP-3a is the known ligand for CCR6. The specification teaches that certain tumors express the chemotaxis factor MIP-3a (page 9, lines 23-27).

The specification teaches abnormal infiltration of IDO+ cells in samples of tumor and tumor-draining lymph nodes from patients with malignant melanoma (pages 48-50). The specification teaches MIP-3a expression in malignant melanoma (pages 51, lines 3-12). The specification never disclosed if the tumor and tumor-draining lymph nodes samples from patients with malignant melanoma expressed receptor CCR6. The purported utility is administering CCR6 antibodies to block the signal between IDO+ APC and tumors expressing MIP-3a (to reduce recruitment of IDO+ APC). Thus, CCR6 receptor expression on IDO+ APC must be available in sufficient quantity and in appropriate context for a reasonable probability of immunorecognition by the CCR6 antibody (administered composition). In addition, an effective administered agent must **selectively inhibit** the recruitment of cells. The specification fails to teach how an administered CCR6 antibody would discern between an IDO+ APC expressing the CCR6 receptor and a non-tolerogenic APC or a different cell expressing the CCR6

receptor. It is unclear if non-tolerogenic APC or other cells in a tumor or tumor-draining lymph node area express CCR6 receptor. The specification fails to teach how one would determine reduced recruitment of IDO+ APC to tumor or tumor-draining lymph nodes *in vivo*. The Examples only disclose the use of a Boyden Chamber (*in vitro*) to discern migration. The specification fails to demonstrate how the reduction of recruitment of IDO+ APC affects the metastasis of a tumor.

The instant claims are not supported by an enabling disclosure because one cannot extrapolate the teachings of the specification to the claimed invention. There is no guidance on or exemplification of any correlation between the instant Examples and a method comprising administering a composition to reduce recruitment of IDO+ APC to a site wherein the site is determined to comprise recruitment of IDO+ APC ***in vivo.*** The *in vitro* experimental data presented is clearly not drawn to subjects with tumors or tumor-draining lymph nodes. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, pg. 3-4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major

Differences *In vitro*). Dermer (Bio/Technology, March 1994, Vol.12, No. 3 pg. 320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the *in vitro* data presented in the specification, it could not be predicted that, in the *in vivo* environment, would be in any way correlated.

Lastly, the administered agent (i.e. CCR6 antibody) must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition the target cell must not have an alternate means of survival despite action at the proper site for the drug. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the Examples, CCR6 antibodies block MIP-3a induced chemotaxis of CCR6+ APC. The CCR6 antibody is in contact with

cells during the entire exposure period (page 53-54). This would not be the case *in vivo*, where exposure at the target site may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half-life of the protein and the *in vitro* tests of record do not sufficiently duplicate the conditions that occur *in vivo*. In addition, the peptide may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the peptide has no effect, circulation into the target area may be insufficient to carry the peptide and a large enough local concentration may not be established.

The specification provides insufficient guidance with regard to theses issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success. Due to the inherent unpredictability in the field and the lack of guidance in the specification regarding the successful application of the claimed methods to humans having naturally occurring tumors or tumor-draining lymph nodes, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the

complex nature of the invention, the contradictory state of the prior art, one of skill in the art would be forced into undue experimentation without a reasonable expectation of success in order to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is indefinite because of the recitation, "...wherein the biological signal..comprises MIP-3a". A signal is a current, image, voltage, etc. A signal may be conveyed, transduced, or transmitted through (or by) MIP-3a. It is unclear how a signal comprises MIP-3a.

Claim 8 recites the limitation "wherein the compound". There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
8/23/06

Marianne P. Allen
PRIMARY EXAMINER
AU1647 8/25/06